CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-061/SE2-007

21-062/SE2-008

ENVIRONMENTAL ASSESSMENT

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

NDA 21-061/SE-007

Tequin®
(Gatifloxacin Tablets; 200 and 400 mg)

Division of Special Pathogen and Immunologic Drug Products
(HFD-590)
Center for Drug Evaluation and Research

Date Completed: October 8, 2001

FINDING OF NO SIGNIFICANT IMPACT

NDA 21-061/SE-007

Tequin®
(gatofloxacin tablets; 200 and 400 mg)

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement is not required.

In support of its supplemental new drug application for Tequin® (gatifloxacin) tablets, Bristol-Meyers Squibb Company has prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts of the use and disposal from use of the product.

This application, NDA 21-061/SE-007, Tequin®, provides for the oral use of this drug for a new indication in the treatment of bronchitis.

Fate information was provided for the drug substance, gatifloxacin. The results indicate that gatifloxacin is expected to undergo considerable degradation via direct photolysis. Due to its physicochemical properties, the gatifloxacin that remains in the environment is likely to partition into the aquatic compartment. Toxicity was evaluated according to the tiered approach to environmental effects testing as specified in the November 1995 guidance entitled Environmental Assessments in Human Drug Applications and Supplements. The results of toxicity studies indicate that the gatifloxacin is not expected to affect organisms at the expected environmental concentrations. Therefore, no adverse environmental effects are expected to result from this action.

Tequin® Tablets will be used primarily by patients in their homes and in hospitals and clinics, through physician prescription. U.S. hospitals, pharmacies, or clinics will dispose of empty or partially empty packages in accordance with their internal waste handling procedures. In the home, disposal will be through community solid waste management systems, which may include landfills, incineration and recycling, although minimal quantities of the unused drug could be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

PREPARED BY
Melissa J. Maust
Chemist, Center for Drug Evaluation and Research

CONCURRED BY
Nancy B. Sager
Environmental Officer, Center for Drug Evaluation and Research

CONCURRED BY
Yuan-yuan Chiu, Ph.D.
Director, Office of New Drug Chemistry, Center for Drug Evaluation and Research

Attachment: Environmental Assessment
Appended Electronic Signature Page

SUPPLEMENTAL NEW DRUG APPLICATION: NDA #21-861
TEQUIN (gatifloxacin) TABLETS

PART IV ENVIRONMENTAL ASSESSMENT

Environmental Assessment

Section 1. Date

August, 2000

Section 2. Name of Applicant/Petitioner

Bristol-Myers Squibb Company

Section 3. Address (Mailing)

5 Research Parkway
Wallingford, CT 06492

Section 4. Description of Proposed Action

a. Requested Approval

Bristol-Myers Squibb is filing a Supplemental New Drug Application (SNDA), NDA #21-061, pursuant to Section 505 (b) of the Federal Food, Drug and Cosmetic Act for Tequin™ (gatifloxacin) Tablets, 200 and 400 mg. This Environmental Assessment (EA) is being submitted pursuant to 21 CFR part 25.

PART IV ENVIRONMENTAL ASSESSMENT

b. Need for Action

Gatifloxacin is a fluoroquinolone antiinfective intended for use by the oral and intravenous routes. This SNDA requests approval for oral use of this drug for a new indication, treatment of bronchitis.

c. Locations of Use

The tablets are sold to hospitals, clinics and pharmacies throughout the USA for use by both in-patient and out-patient populations. The intravenous formulation is used primarily in hospitals.

d. Disposal Sites

At U.S. hospitals, clinics and pharmacies empty, or partially empty, containers will be disposed of according to the facility's procedures. Empty or partially empty containers from homes of patients will typically be disposed of by a community's solid waste management system that could include landfills, incineration and/or recycling. Minimal quantities of unused drug could be disposed of in sewer systems.

SUPPLEMENTAL NEW DRUG APPLICATION: NDA #21-061
TEQUIN (gatifloxacin) TABLETS

PART IV ENVIRONMENTAL ASSESSMENT

Section 5 Identification of Substances that Are the Subject of the Proposed Action

This SNDA is for Tequin™ Tablets. The relevant drug substance and active ingredient is gatifloxacin.

a. Nomenclature

i. Established Name (U.S. Adopted Name - USAN)

Gatifloxacin

ii. Brand/Proprietary Name/Tradename

Tequin™

iii. Chemical Names

Chemical Abstracts (CA) Index Name

(±)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid, sesquihydrate

b. Chemical Abstracts Service (CAS) Registration Number

180200-66-2

SUPPLEMENTAL NEW DRUG APPLICATION: NDA #21-061
TEQUIN (gatifloxacin) TABLETS

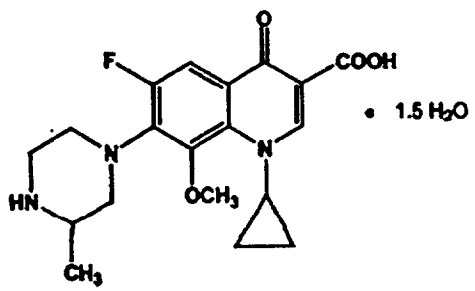
PART IV ENVIRONMENTAL ASSESSMENT

c/d. **Molecular Formulas and Molecular Weights**

Molecular Formula is: $C_{19}H_{22}FN_3O_4 \cdot 1.5H_2O$

Molecular Weight is: 402.42

e. **Structural (graphic) Formula**



SUPPLEMENTAL NEW DRUG APPLICATION: NDA #21-861
TEQUIN (gatifloxacin) TABLETS

PART IV ENVIRONMENTAL ASSESSMENT

Section 6 Environmental Issues

a. Environmental Fate of Released Substances

i. Identification of Substances of Interest

Gatifloxacin used for pharmaceutical production must contain less than 2 % total impurities, exclusive of water. The drug is not metabolized in humans to any significant extent (Ref. 1,2), so that the substance excreted into the environment through patient therapy is gatifloxacin itself. Approximately 70-90% of the drug is excreted unchanged in the urine over a 72 hour period (Ref. 1-5), with 5-6% excreted unchanged in the feces (Ref. 1, 2). Gatifloxacin is therefore the subject of the following discussion. The information concerning the metabolic fate of gatifloxacin, and the referenced documents were detailed in the original NDA and will not be elaborated further here. Copies of the abstracts of the metabolism studies are appended here for the convenience of the reviewer.

ii. Physical and Chemical Characterization

Basic physicochemical properties of gatifloxacin are summarized in the data table of the Non-confidential Appendix. Gatifloxacin is somewhat water-soluble and ionizable compound. It has a very low octanol/water partition coefficient. It is a solid substance at room temperature and is expected to have negligible vapor pressure at ambient temperature. Based on this information, the drug is expected to distribute to the aqueous compartment.

PART IV ENVIRONMENTAL ASSESSMENT

iii. Environmental Depletion Mechanisms

Studies to develop this data were conducted according to the FDA Environmental Assessment Technical Assistance Handbook, under GLP regulations, at Springborn Laboratories, Wareham, MA, under the sponsorship of Bristol-Myers Squibb Company. Analytical methods were validated as per requirements.

Since gatifloxacin is a fluoroquinolone, it was expected to undergo degradation primarily by photolysis. The results of the photolysis study (Ref. 6) are summarized in the data table of the Non-confidential Appendix. Based on this data, gatifloxacin is degraded relatively rapidly when exposed to light.

iv. Environmental Concentrations

Based on estimated 5-year production volumes, the Maximum Expected Environmental Concentration (MEEC) has been estimated for the aqueous compartment, according to the guidance provided by the FDA in July, 1998 (Ref. 7). This MEEC is equivalent to the Expected Introduction Concentration (EIC). It should be noted that the Expected Environmental Concentration (ECC) is likely to be at least 10-fold lower than this due to dilution of water exiting publicly owned treatment works (POTWs). A factor of 10-fold has been used to account for this dilution. In addition, some degradation as a result of photolytic breakdown is expected and can result in an even lower EEC. The calculations for the EIC and EEC are shown in the Confidential Appendix 1.

PART IV ENVIRONMENTAL ASSESSMENT

v. Summary

Gatifloxacin in the environment is expected to undergo considerable degradation based on the data from the direct photolysis study. It is not a volatile substance and is not expected to enter the atmospheric compartments. Gatifloxacin is somewhat water-soluble and partitions much more to aqueous vs. organic solutions. If it enters the environment it is most likely to remain in the aquatic environment. The maximum expected environmental concentration (MEEC) is found in Confidential Appendix 1.

b. Environmental Effects of Released Substances

i. Tiered Approach to Environmental Effects Testing

The data of the indirect photolysis study suggest that considerable degradation of gatifloxacin may occur by photolytic mechanisms, with a projected environmental half-life of less than one day at pH 7 and pH 9. The predicted environmental half-life was somewhat longer at pH 5, approximately 1.9 days. However, there can be considerable fluctuation in light intensity in the environment and we have not attempted to modify the EIC based on the photodegradation data. Since the compound has a very low log Kow and is distributed to the water compartment, data concerning microbial inhibition and acute toxicity to aquatic species (Daphnia magna) were developed and reviewed (Tier 1). In addition, since acute toxicity for bluegills was also available, this was also reviewed (Tier 2 - partial).

ii. Microbial Inhibition

The potential for gatifloxacin to affect wastewater treatment microorganisms was assessed using microbial inhibition studies (Ref. 8). The results of these studies indicated considerable variation in the susceptibility of the organisms to gatifloxacin, with MICs ranging from 0.05 ppm to >1000 ppm. Bacillus and Nostoc were most susceptible with MICs of 0.05 ppm. These results are not surprising since the drug is a broad spectrum fluoroquinolone antibiotic. These data are summarized in the data table of the Non-confidential Appendix.

iii. Tier 1-2 Acute Toxicity to Aquatic Species

The data table of the Non-confidential Appendix also contains a summary of the results of the aquatic toxicity studies on Daphnia magna and bluegills (Ref. 9, 10). Both the fish and the Daphnia were quite resistant to gatifloxacin with considerable margins between the MEEC and the no observed effect concentration (NOEC).

iv. Test Methods and Test Organisms

The microbial inhibition and aquatic toxicity studies described above were performed using test organisms and methods in accordance with the guidance provided in the FDA Environmental Assessment Technical Assistance Handbook (Ref. 11), under GLP regulations, at Springborn Laboratories, Wareham, MA, under the sponsorship of Bristol-Myers Squibb Company.

SUPPLEMENTAL NEW DRUG APPLICATION: NDA #21-061
TEQUIN (gatifloxacin) TABLETS

PART IV ENVIRONMENTAL ASSESSMENT

c. **Summary of Environmental Fate and Effects**

Gatifloxacin is expected to undergo considerable degradation via direct photolysis. Due to its physicochemical properties, gatifloxacin that remains in the environment is likely to partition into the aquatic compartment. Relative to the results of the ecotoxicological studies, there was a margin of at least 100,000-fold between the estimated MEEC (equal to EIC) and the values obtained for NOEC, and/or EC50. Smaller margins were noted between MICs for certain susceptible species of microorganisms and the estimated MEEC. Since mixed cultures of microorganisms are typical for most POTWs, at the projected volumes a significant impact on their functioning is not expected. Therefore it is anticipated that the projected volumes of gatifloxacin will not pose a significant risk of harm to aquatic organisms or to the microorganisms at POTWs.

Section 7 Mitigation Measures

As significant adverse environmental effects are not predicted, mitigation measures are not warranted.

Section 8 Alternatives to the Proposed Action

Since significant environmental effects are not predicted to occur, and since mitigation measures are not proposed, consideration of alternatives to the proposed action is not necessary.

SUPPLEMENTAL NEW DRUG APPLICATION: NDA #21-061
TEQUIN (gatifloxacin) TABLETS

PART IV ENVIRONMENTAL ASSESSMENT

Section 9 List of Preparers

Eileen Hayes, Sc.D., DABT, Associate Director, Occupational & Environmental Toxicology, has been a practicing toxicologist since 1979 with experience in occupational and environmental toxicology and chemical metabolism. She received the B.S. in Pharmacy from Northeastern University, the Sc.D. in Toxicology from Harvard School of Public Health and post-doctoral training at Brigham & Women's Hospital/ Harvard Medical School.

SUPPLEMENTAL NEW DRUG APPLICATION: NDA #21-061
TEQUIN (gatifloxacin) TABLETS

PART IV ENVIRONMENTAL ASSESSMENT

Section 10 References

1. Gajjar, D. A., Oral Dose Phase I Study of Gatifloxacin, Nov. 20, 1998, Bristol-Myers Squibb Internal Document # 910072083.

2. Grasela, D.M., et al., Phase 1 Trial of a Single Intravenous Infusion of DMS 206584 (AM-1155) in Healthy Male Volunteers. Clinical Report Synopsis, September 13, 1996, Bristol-Myers Squibb Internal Document # 910058297.

3. Grasela, D.M., et al., Pharmacokinetics of BMS 206584; 200 mg Oral Dose with *Probenecid* in Humans, Clinical Report Synopsis, September 13, 1996, Bristol-Myers Squibb Internal Document # 910058296.

4. Grasela, D.M., et al., Randomized, Double-Blind, Placebo-Controlled, Single-Dose Followed by Multiple-Dose, Dose Escalation Study of the Safety, Tolerance, and Pharmacokinetics of Intravenous Gatifloxacin in Healthy Subjects, October 14, 1998, Bristol-Myers Squibb Internal Document # 910070260.

5. Grasela, D.M., et al., 300 mg Oral Multiple Dose Phase I Study of BMS 206584, Clinical Report Summary, September 13, 1996, Bristol-Myers Squibb Internal Document # 910058298.

6. McLaughlin, S., Gatifloxacin – Photodegradation in Water Using Artificial Sunlight, SLI Report #98-9-7492 December 2, 1998

7. Guidance for Industry: Environmental Assessments of Human Drug and Biologics Applications. U.S. Department of Health and Human Services, Food and Drug Administration. July, 1998.

8. Gledhill, W.B., Gatiloxacin – Determination of Microbial Growth Inhibition, SLI Report #98-6-7360. August 18, 1998,

9. Collins, M., Gatifloxacin – Acute Toxicity to Daphnids under Static Conditions, SLI Report #98-6-7358, October 19, 1998.

10. Collins, M., Gatifloxacin – Acute Toxicity to Bluegill Sunfish under Static-Renewal Conditions, SLI Report #98-6-7351, October 21, 1998.

11. Erikson, C. et al., Environmental Assessment Technical Assistance Handbook, Food and Drug Administration, March,1987.

SUPPLEMENTAL NEW DRUG APPLICATION: NDA #21-061
TEQUIN (gatifloxacin) TABLETS

PART IV ENVIRONMENTAL ASSESSMENT

12. Gatifloxacin – Drug Master File (DMF) 13902, Kyorin Pharmaceutical Co. Ltd.

SUPPLEMENTAL NEW DRUG APPLICATION: NDA #21-061
TEQUIN (gatifloxacin) TABLETS

PART IV ENVIRONMENTAL ASSESSMENT

Section 11 Appendices

One nonconfidential appendix and two confidential appendices follow.

SUPPLEMENTAL NEW DRUG APPLICATION: NDA #21-061
TEQUIN (gatifloxacin) TABLETS

PART IV ENVIRONMENTAL ASSESSMENT

NONCONFIDENTIAL APPENDIX 1
Data Summary Table

SUPPLEMENTAL NEW DRUG APPLICATION: NDA #21-061
TEQUIN (gatifloxacin) TABLETS

PART IV ENVIRONMENTAL ASSESSMENT

NONCONFIDENTIAL APPENDIX 1

DATA SUMMARY TABLE

Physical/Chemical Characterization	
Water solubility (Ref. 12)	0.12%
Ionization constants (Ref. 12)	pKa1 = 5.94; pKa2 = 9.21;
Partition coefficient - Kow (octanol/water); [Log Kow] (Ref. 12)	At pH = 5.1 Kow = 0.044 [log Kow = -1.3565] At pH = 7.0 Kow = 0.145 [log Kow = -0.8386] At pH = 8.9 Kow = 0.119 [log Kow = -0.9245]
Vapor Pressure	virtually nil
Depletion Mechanisms	
Photolysis (Ref. 6)	Predicted half-lives: $T_{1/2}$ at pH 5 = 3.75 days (experimental) = 1.88 days (environmental) $T_{1/2}$ at pH 7 = 1.93 days (experimental) = 0.97 days (environmental) $T_{1/2}$ at pH 9 = 1.65 days (experimental) = 0.83 days (environmental)
Environmental Effects	
Microbial Inhibition: (Ref. 8)	
Aspergillus niger and *Tricoderma viride*	*No inhibition @ 1000 ppm*
Clostridium perfringens	MIC = 0.15 ppm
Bacillus subtilis and Nostoc sp.	MIC = 0.05 ppm
Daphnia Magna Acute Toxicity (48 hr.) (Ref. 9)	NOEC = 120 mg/l; EC50 = 350 mg/l
Fish Acute Toxicity (Bluegills) (96 hr.) (Ref. 10)	NOEC = 540 mg/l; EC50 = 930 mg/l

Abbreviations used in the Table:

NOEC = No observed effects concentration
MIC = Minimum inhibitory concentration
EC50 = Concentration producing 50% immobilization
LC50 = Concentration producing death in 50% of the test group

Physical Characteristic	Value	Summary of the Analytical Test Method
Aqueous Solubility (at 25° ± 0.5°C)	1.2 mg/mL ("0.12%")	Spectrophotometric Method. - Shake finely divided gatifloxacin in water for several days at 25° ± 0.5°C. Filter to remove insoluble drug. Dilute filtrate with 0.1 M NaOH to prepare samples. Measure absorbance of samples (spectrophotometer, 289 nm; 1 cm cell). Compare absorbance to curve prepared using solutions of known gatifloxacin concentration.
Ionization Constant (pKa)	$pKa_1 = 5.94$ $pKa_2 = 9.21$	Potentiometric Titration Method. - By definition, pKa is the pH at which equimolar concentrations of dissociated and undissociated gatifloxacin are present in solution (i.e. : pH at midpoint of the titration curve). Gatifloxacin has two pKa values, determined as follows. Dissolve gatifloxacin in water. Titrate (potentiometric titrator) solution aliquots at 25° ± 0.5°C using 0.1 M HCl and 0.1 M NaOH. Determine pKa_1 from the HCl titration curve, and pKa_2 from the NaOH titration curve.
Octanol-Water Partition Ratio (K o/w)	at pH / K o/w 5.1 / 0.044 7.0 / 0.145 8.9 / 0.119	Liquid / Liquid Partition Method. - Dissolve gatifloxacin in measured volumes of "Britton-Robinson" buffers (pH 5.1, 7.0, and 8.9). To each buffer, add equal volume of 1-octanol and agitate for several hours at 25° ± 0.5°C. Centrifuge to separate the water and octanol layers and sample each layer. Dilute aqueous layer samples with 0.1 N NaOH, and (to same extent) the 1-octanol layer samples with 1-octanol. Measure absorbance of samples (spectrophotometer, 289 nm; 1 cm cell). Compare absorbance to curve prepared using solutions of known gatifloxacin concentration.
Vapor Pressure	Virtually nil.	A vapor pressure study was not conducted. Based on the high melting temperature (184 degrees C) the compound is considered to have low volatility. It is expected to partition primarily into the aquatic compartment vs. the atmospheric compartment.

In an Oct. 9, 21 fax from the firm, permission was given to add this table to the EA as a non-confidential section that may be released under FOI.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Melissa Maust
10/10/01 10:35:14 AM

Nancy Sager
10/10/01 11:16:31 AM

Yuan-Yuan Chiu
10/10/01 02:42:20 PM
concurred

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 21-061/SE-007

Tequin™

(Gatifloxacain Tablets; 200 and 400 mg)

Division of Special Pathogen and Immunologic Drug Products
(HFD-590)
Center for Drug Evaluation and Research

Date Completed: August 23, 2001

EXECUTIVE SUMMARY – ENVIRONMENTAL ASSESSMENT

A FONSI is not recommended. Additional information is needed.

NDA 21-061 provides for Gatifloxan is a fluoroquniolone anti-infective intended for use via oral and intravenous routes. This supplemental NDA requests approval for oral use of this drug for a new indication in the treatment of bronchitis.

Gatifloxacin is expected to undergo considerable degradation via direct photolysis. Due to its physicochemical properties, the gatifloxacin that remains in the environment is likely to partition into the aquatic compartment. Relative to the results of the ecotoxicological studies, there was a margin of at least 100,000-fold between the estimated MEEC (equal to EIC) and the values obtained for NOEC, and/or EC50. Smaller margins were noted between MICs for certain susceptible species of microorganisms and the estimated MEEC. Since mixed cultures of miroorganisms are typical for most POTWs, a significant impact on their functioning is not expected at the projected volumes.

APPEARS THIS WAY
ON ORIGINAL

REVIEW - ENVIRONMENTAL ASSESSMENT

1. **Date:**

   EA dated: August 2000

   PM: Diana Willard

2. **Name of applicant/petitioner:**

   Bristol-Myers Squibb Company

   ADEQUATE

3. **Address:**

   5 Research Parkway
   Wallingford, CT 06492

   ADEQUATE

4. **Description of the proposed action:**

   a. **Requested Approval:**

      Bristol-Meyers Squibb is filing a supplement New Drug Application (SNDA), 21-061, pursuant to section 505b of the FD&C Act for Tequin™ (gatifloxacin), 200 and 400 mg tablets. This Environmental Assessment (EA) is being submitted pursuant to 21 CFR part 25.

      ADEQUATE

   b. **Need for Action:**

      Gatifloxan is a fluoroquniolone antiinfective intended for use by the oral and intravenous routes. This SNDA requests approval for oral use of this drug for a new indication, treatment of bronchitis.

      ADEQUATE

c. **Expected Locations of Use (Drug Product):**

The tablets are sold to hospitals, clinics and pharmacies throughout the USA for use by both in-patient and out-patient populations. The intravenous formulation is used primarily in hospitals.

ADEQUATE

d. **Disposal Sites**

At U.S. hospitals, pharmacies and clinics, empty or partially empty containers will be disposed of according to the facility's procedures. In the home, empty or partially empty containers will typically be disposed of by the community's solid waste management system, which may include landfills, incineration and recycling. Minimal quantities of the unused drug may potentially be disposed of directly into the sewer system.

ADEQUATE

5. **Identification of chemical substances that are the subject of the proposed action**:

Drug Substance: USAN: Gatifloxacin
Brand/Proprietary: Tequin™

Chemical Name: (±)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid, sesquihydrate

CAS #: 180200-66-2
Molecular Weight: 402.42
Molecular Formula: $C_{19}H_{22}FN_3O_4 \cdot 1.5\ H_2O$
Structural Formula: Provided on Page 7 of the EA

ADEQUATE

6. **Environmental Issues**:

a. **Identification of Substances of Interest**

Gatifloxacin used for pharmaceutical production must contain less than 2% total impurities, exclusive of water. The drug is not metabolized in humans to any significant extent. Therefore, the substance excreted into

the environment through patient therapy is gatifloxacin itself. Approximately 70-90% of the drug is excreted unchanged in the urine over a 72 hour period, with 5-6% excreted unchanged in the feces.

The firm makes reference to the original NDA for detailed information of the metabolic fate of gatifloxacin. The firm has attached copies of the abstracts of the metabolism study to this EA.

ADEQUATE

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

b. Environmental Fate of Released Substances: Physical and Chemical Characterization

Test	*Result*
Physical/Chemical Characterization	
Water solubility (Ref. 12)	0.12%
Ionization constants (Ref. 12)	pKa1 = 5.94; pKa2=9.21
Partition Coefficient - K_{ow}(octanol/water); [Log Kow] (Ref. 12)	at pH = 5.1, Kow = 0.044 [log Kow = -1.3565] at pH = 7.0, Kow = 0.145 [log Kow = -0.8386] at pH = 8.9, Kow = 0.119 [log Kow = -0.9245]
Vapor Pressure	Virtually nil
Depletion Mechanisms	
Photolysis (Ref. 6)	Predicted half-lives: T ½ at pH 5 = 3.75 days (experimental) = 1.88 days (environmental) T ½ at pH 7 = 1.93 days (experimental) = 0.97 days (environmental) T ½ at pH 5 = 1.65 days (experimental) = 0.83 days (environmental)
Environmental Effects	
Microbial Inhibition (ref. 8) Aspergillus niger and Tricoderma viride Clostridium perfringens Bacillus subtilis and Nostoc sp.	 No inhibition @ 1000 ppm MIC = 0.15 ppm MIC = 0.05 ppm
Daphnia Magna Acute Toxicity (48hr.) (Ref. 9)	NOEC = 120 mg/l; EC_{50} = 350 mg/l **(see comments in boldin section 6.d.)**
Fish Acute Toxicity (Bluegills)(96 hr.) (Ref. 10)	NOEC = 540 mg/l; EC_{50} = 930 mg/l **(see comments in bold in section 6.d.)**

With respect to the information provided in the EA for the test methods for the water solubility, ionization constants, partition coefficient, and vapor pressure, the firm needs to provide a brief description of the tests as per the EA guidance section IV.D. To the firm: **With respect to Section IV.D. of the July 1998 guidance entitled Environmental Assessment of Human Drug and Biologics Applications, please revise the EA (specifically for the water solubility, ionization constant, partition coefficient, and vapor pressure) so that the environmental assessment includes a description of the test method. The reference to the drug master file is not sufficient. The test method description should be sufficient for a reviewer to determine the scientific merit of the methodology. For example, the methodology used to determine water solubility should be identified, along with the temperature and pH at which the solubility was determined. If actual studies were not done (e.g., vapor pressure), please provide the basis for the statements.**

Based on the information provided in the table, it shows that gatifloxacin is somewhat water soluble and ionizable compound. It has a very low octanol/water partition coefficient. It is expected to have negligible vapor pressure at ambient temperature. Based on this information, the drug is expected to distribute to the aqueous compartment. However, since the firm does not provide the description of the test methods for these physical properties, it is not clear how these statements can be made.

DEFICIENT; comment in bold will be communicated to the firm

c. **Environmental Depletion Mechanisms**

Studies to develop this data were conducted according to the FDA Environmental Assessment Technical Assistance Handbook, under GLP regulations, at Springborn Laboratories, Wareham, MA, under the sponsorship of Bristol-Meyers Squibb Company. Analytical Methods were validated as per the requirements.

Since gatifloxacin is a fluoroquinolone and is expected to undergo degradation primarily by photolysis. Gatifloxacin is degraded relatively rapidly when exposed to light.

ADEQUATE

c. Environmental concentration

Based on estimated 5-year production volumes of 47,400 kg/yr, the Maximum Expected Environmental Concentration (MEEC) has been [redacted] in accordance with the July 1998 EA guidance. This MEEC is equivalent to the Expected Introduction Concentration (EIC) since this is the higher concentration of the EIC vs. EEC (Expected Environmental Concentration). [redacted]

The calculations for the EIC, EEC, and MEEC are contained in Confidential Appendix 1 with the results as follows:

[redacted]

Gatifloxacin in the environment is expected to undergo considerable degradation based on the data from the direct photolysis study. It is not a volatile substance and is not expected to enter the atmospheric compartments. It is somewhat water-soluble and partitions much more to aqueous instead of organic solution. The firm speculates that if it enters the environment, it is most likely to remain in the aquatic environment.

ADEQUATE

d. Environmental Effects:

The data of the indirect photolysis study suggest that considerable degradation of gatifloxacin may occur by photolytic mechanisms, with a projected environmental half-life of less than one day at pH 7 and pH 9. The predicted environmental half life was somewhat longer at pH 5, approximately 1.9 days. The firm states that there can be considerable fluctuation in light intensity in the environment. The have not attempt to modify the EIC based on the photodegradation data.

Since the compound has a very low Kow and is distributed to the water compartment, data concerning microbial inhibition and acute toxicity to

aquatic species (daphnia magna) were developed (Tier 1 of EA guidance). In addition, since acute toxicity for bluegills was also available, this was also evaluated (Tier 2 – partial).

Microbial Inhibition: The potential for gatifloxacin to affect wastewater treatment microorganisms was assessed using microbial inhibition studies (Ref. 8). The results of these studies indicated considerable variation in the susceptibility of the organisms to gatifloxacin, with MIC's ranging from 0.05 ppm to > 1000 ppm. Bacillus and Nostoc were most susceptible with MICs of 0.05 ppm. Since the drug is a broad spectrum of fluoroquinolone antibiotic, this is not unexpected. The data are summarized in a data table in the non-confidential appendix.

Acute Toxicity to Aquatic Species: The data table in the non-confidential appendix also contains a summary of the results of the aquatic toxicity studies on daphnia magna and bluegills (Ref. 9, 10). Both the fish and the daphnia were resistant to gatifloxacin as seen with considerable margins between the MEEC and the NOEC (no observed effect concentration).

The microbial inhibition and aquatic toxicity studies were performed using test organisms and methods in accordance with the guidance provided in the FDA Environmental Assessment Technical Assistance Handbook (Ref. 100), under GLP regulations, at Springborn Laboratories, Wareham, MA.

7. Mitigation Measures

As significant adverse environmental effects are not predicted, mitigation measures are not warranted.

ADEQUATE

8. Alternatives to the proposed action

Since significant environmental effects are not predicted to occur, and since mitigation measures are not proposed, considerations of alternatives to the proposed action is not necessary.

ADEQUATE

9. List of Preparers

Name and credentials for the person responsible for preparing this EA is provided on page 13.

ADEQUATE

10. References

References are provided for the test methods used from the FDA Environmental Assessment Technical Handbook, the environmental assessment guidance for industry, and several articles relating to this drug substance.

ADEQUATE

11. Appendices

On page 3 of the EA, you make the following statement: "Portions of the environmental assessment, including the appendices, are considered confidential by Bristol-Meyers Squibb Company, and should not be released under the Freedom of Information (FOI) Act. A separate, nonconfidential report releaseable under FOI is also provided." However, it is not clear what part of the submitted EA are confidential and nonconfidential. Please clearly identify the parts of the EA you consider nonconfidential when submitting the revised EA.

DEFICIENT; comment in bold will be communicated to the firm

DEFICIENCY LIST – ENVIRONMENTAL ASSESSMENT (EA)
ANDA 21-061/S-007

The following deficiencies pertain to the environmental assessment (EA) dated August 2000. Please provide a revised EA that incorporates the changes. The appendices need not be resubmitted if there are no changes in them.

1. With respect to Section IV.D. of the July 1998 guidance entitled Environmental Assessment of Human Drug and Biologics Applications, please revise the EA (specifically for the water solubility, ionization constant, partition coefficient, and vapor pressure) so that the environmental assessment includes a description of the test method. The reference to the drug master file is not sufficient. The test method description should be sufficient for a reviewer to determine the scientific merit of the methodology. For example, the methodology used to determine water solubility should be identified, along with the temperature and pH at which the solubility was determined. If actual studies were not done (e.g., vapor pressure), please provide the basis for the statements.

2. The confidential appendices indicate that the acute toxicity results are on the active ingredient basis, however, it is not clear from the data provided in the summary table whether or not the acute toxicity studies are based on the active ingredient as opposed to the hydrate. Please clarify and update the appropriate sections in the EA to reflect this calculation.

3. On page 3 of the EA, you make the following statement: "Portions of the environmental assessment, including the appendices, are considered confidential by Bristol-Meyers Squibb Company, and should not be released under the Freedom of Information (FOI) Act. A separate, nonconfidential report releaseable under FOI is also provided." However, it is not clear what part of the submitted EA are confidential and nonconfidential. Please clearly identify the parts of the EA you consider nonconfidential when submitting the revised EA.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Melissa Maust
8/27/01 07:17:51 AM
ENV ASSESSMENT
A FONSI is not recommended until the firm addresses the deficiencies.
The deficiencies are listed at the end of the review.
The PM will be asked to communicate the deficiencies to the firm.

Nancy Sager
8/27/01 07:29:40 AM
ENV ASSESSMENT
Concur

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 21-061/SE-007

Tequin™

(Gatifloxacain Tablets; 200 and 400 mg)

Division of Special Pathogen and Immunologic Drug Products
(HFD-590)
Center for Drug Evaluation and Research

Date Completed: October 8, 2001

EXECUTIVE SUMMARY – ENVIRONMENTAL ASSESSMENT

A FONSI is recommended.

NDA 21-061 provides for Gatifloxan is a fluoroquniolone anti-infective intended for use via oral and intravenous routes. This supplemental NDA requests approval for oral use of this drug for a new indication in the treatment of bronchitis.

Gatifloxacin is expected to undergo considerable degradation via direct photolysis. Due to its physicochemical properties, the gatifloxacin that remains in the environment is likely to partition into the aquatic compartment. Relative to the results of the ecotoxicological studies, there was a margin of at least 100,000-fold between the estimated MEEC (equal to EIC) and the values obtained for NOEC, and/or EC50. Smaller margins were noted between MICs for certain susceptible species of microorganisms and the estimated MEEC. Since mixed cultures of miroorganisms are typical for most POTWs, a significant impact on their functioning is not expected at the projected volumes.

APPEARS THIS WAY
ON ORIGINAL

REVIEW - ENVIRONMENTAL ASSESSMENT

1. Date:

EA dated: August 2000
Amendment: October 2, 2001

PM: Diana Willard

ADEQUATE

2. Name of applicant/petitioner:

Bristol-Myers Squibb Company

ADEQUATE

3. Address:

5 Research Parkway
Wallingford, CT 06492

ADEQUATE

4. Description of the proposed action:

a. Requested Approval:

Bristol-Meyers Squibb is filing a supplement New Drug Application (SNDA), 21-061, pursuant to section 505b of the FD&C Act for Tequin™ (gatifloxacin), 200 and 400 mg tablets. This Environmental Assessment (EA) is being submitted pursuant to 21 CFR part 25.

ADEQUATE

b. Need for Action:

Gatifloxan is a fluoroquniolone antiinfective intended for use by the oral and intravenous routes. This SNDA requests approval for oral use of this drug for a new indication, treatment of bronchitis.

ADEQUATE

c. Expected Locations of Use (Drug Product):

The tablets are sold to hospitals, clinics and pharmacies throughout the USA for use by both in-patient and out-patient populations. The intravenous formulation is used primarily in hospitals.

ADEQUATE

d. Disposal Sites

At U.S. hospitals, pharmacies and clinics, empty or partially empty containers will be disposed of according to the facility's procedures. In the home, empty or partially empty containers will typically be disposed of by the community's solid waste management system, which may include landfills, incineration and recycling. Minimal quantities of the unused drug may potentially be disposed of directly into the sewer system.

ADEQUATE

5. **Identification of chemical substances that are the subject of the proposed action:**

Drug Substance: USAN: Gatifloxacin
Brand/Proprietary: Tequin™

Chemical Name: (±)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid, sesquihydrate
CAS #: 180200-66-2
Molecular Weight: 402.42
Molecular Formula: $C_{19}H_{22}FN_3O_4 \cdot 1.5\ H_2O$
Structural Formula: Provided on Page 7 of the EA

ADEQUATE

6. **Environmental Issues:**

a. Identification of Substances of Interest

Gatifloxacin used for pharmaceutical production must contain less than 2% total impurities, exclusive of water. The drug is not metabolized in humans to any significant extent. Therefore, the substance excreted into the environment through patient therapy is gatifloxacin itself. Approximately 70-90% of the drug is excreted unchanged in the urine over a 72 hour period, with 5-6% excreted unchanged in the feces.

The firm makes reference to the original NDA for detailed information of the metabolic fate of gatifloxacin. The firm has attached copies of the abstracts of the metabolism study to this EA.

ADEQUATE

b. Environmental Fate of Released Substances: Physical and Chemical Characterization

Test	*Result*
Physical/Chemical Characterization	
Water solubility (Ref. 12)	0.12% [redacted]
Ionization constants [redacted] (Ref. 12)	pKa1 = 5.94; pKa2=9.21
Partition Coefficient - K_{ow}(octanol/water); [Log Kow] [redacted] (Ref. 12)	at pH = 5.1, Kow = 0.044 [log Kow = -1.3565] at pH = 7.0, Kow = 0.145 [log Kow = -0.8386] at pH = 8.9, Kow = 0.119 [log Kow = -0.9245]
Vapor Pressure	Virtually nil. [redacted]
Depletion Mechanisms	
Photolysis (Ref. 6)	Predicted half-lives: $T_{½}$ at pH 5 = 3.75 days (experimental) = 1.88 days (environmental)

	T ½ at pH 7 = 1.93 days (experimental) = 0.97 days (environmental) T ½ at pH [redacted] = 1.65 days (experimental) = 0.83 days (environmental)
Environmental Effects	
Microbial Inhibition (ref. 8) [redacted] Aspergillus niger and Tricoderma viride Clostridium perfringens Bacillus subtilis and Nostoc sp.	 No inhibition @ 1000 ppm MIC = 0.15 ppm MIC = 0.05 ppm
Daphnia Magna Acute Toxicity (48hr.) (Ref. 9)	NOEC = 120 mg/l; EC_{50} = 350 mg/l **(data expressed as anhydrous drug)**
Fish Acute Toxicity (Bluegills)(96 hr.) (Ref. 10)	NOEC = 540 mg/l; EC_{50} = 930 mg/l **(data expressed as anhydrous drug)**

[redacted]

[redacted]

ADEQUATE

c. **Environmental Depletion Mechanisms**

Studies to develop this data were conducted according to the FDA Environmental Assessment Technical Assistance Handbook, under GLP regulations, at Springborn Laboratories, Wareham, MA, under the sponsorship of Bristol-Meyers Squibb Company. Analytical Methods were validated as per the requirements.

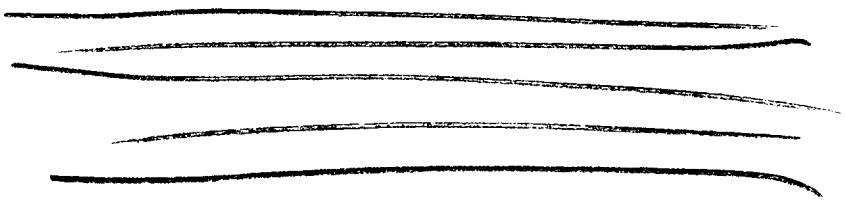
Since gatifloxacin is a fluoroquinolone and is expected to undergo degradation primarily by photolysis. Gatifloxacin is degraded relatively rapidly when exposed to light.

ADEQUATE

c. **Environmental concentration**

Based on estimated 5-year production volumes of 47,400 kg/yr, the Maximum Expected Environmental Concentration (MEEC) has been [redacted] in accordance with the July 1998 EA guidance. This MEEC is equivalent to the Expected Introduction Concentration (EIC) since this is the higher concentration of the EIC vs. EEC (Expected Environmental Concentration). [redacted]

[redacted]



Gatifloxacin in the environment is expected to undergo considerable degradation based on the data from the direct photolysis study. It is not a volatile substance and is not expected to enter the atmospheric compartments. It is somewhat water-soluble and partitions much more to aqueous instead of organic solution. The firm speculates that if it enters the environment, it is most likely to remain in the aquatic environment.

ADEQUATE

d. **Environmental Effects:**

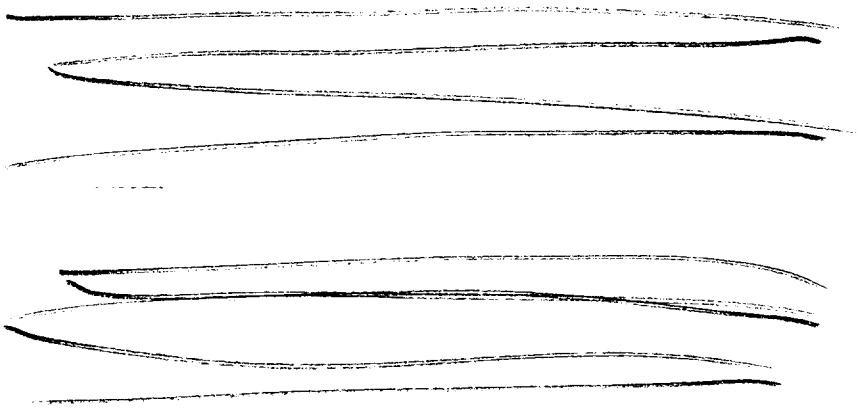
The data of the indirect photolysis study suggest that considerable degradation of gatifloxacin may occur by photolytic mechanisms, with a projected environmental half-life of less than one day at pH 7 and pH 9. The predicted environmental half life was somewhat longer at pH 5, approximately 1.9 days. The firm states that there can be considerable fluctuation in light intensity in the environment. The have not attempt to modify the EIC based on the photodegradation data.

Since the compound has a very low Kow and is distributed to the water compartment, data concerning microbial inhibition and acute toxicity to aquatic species (daphnia magna) were developed (Tier 1 of EA guidance). In addition, since acute toxicity for bluegills was also available, this was also evaluated (Tier 2 – partial).

Microbial Inhibition: The potential for gatifloxacin to affect wastewater treatment microorganisms was assessed using microbial inhibition studies (Ref. 8). The results of these studies indicated considerable variation in the susceptibility of the organisms to gatifloxacin, with MIC's ranging from 0.05 ppm to > 1000 ppm. Bacillus and Nostoc were most susceptible with MICs of 0.05 ppm. Since the drug is a broad spectrum of fluoroquinolone antibiotic, this is not unexpected. The data are summarized in a data table in the non-confidential appendix.

Acute Toxicity to Aquatic Species: The data table in the non-confidential appendix also contains a summary of the results of the aquatic toxicity

studies on daphnia magna and bluegills (Ref. 9, 10). Both the fish and the daphnia were resistant to gatifloxacin as seen with considerable margins between the MEEC and the NOEC (no observed effect concentration).



The microbial inhibition and aquatic toxicity studies were performed using test organisms and methods in accordance with the guidance provided in the FDA Environmental Assessment Technical Assistance Handbook (Ref. 100), under GLP regulations, at Springborn Laboratories, Wareham, MA.

ADEQUATE

7. **Mitigation Measures**

As significant adverse environmental effects are not predicted, mitigation measures are not warranted.

ADEQUATE

8. **Alternatives to the proposed action**

Since significant environmental effects are not predicted to occur, and since mitigation measures are not proposed, considerations of alternatives to the proposed action is not necessary.

ADEQUATE

9. **List of Preparers**

Name and credentials for the person responsible for preparing this EA is provided on page 13.

ADEQUATE

10. References

References are provided for the test methods used from the FDA Environmental Assessment Technical Handbook, the environmental assessment guidance for industry, and several articles relating to this drug substance.

ADEQUATE

11. Appendices

On page 3 of the EA, you make the following statement: "Portions of the environmental assessment, including the appendices, are considered confidential by Bristol-Meyers Squibb Company, and should not be released under the Freedom of Information (FOI) Act. A separate, nonconfidential report releaseable under FOI is also provided." However, it is not clear what part of the submitted EA are confidential and nonconfidential. Please clearly identify the parts of the EA you consider nonconfidential when submitting the revised EA.

In the October 2, 2001 amendment, the firm clarifes that the first 19 pages of the EA are non-confidential and the remainer of the EA (volume 3, pages 20-301) are confidential. This consists of Confidential Appendix 1-Production Volumes and Expected Environmental Concentrations and Confidential Appendix 2-Reference Proprietary Documents (i.e., study reports).

ADEQUATE

DEFICIENCY LIST – ENVIRONMENTAL ASSESSMENT (EA)
ANDA 21-061/S-007

FIRM'S RESPONSE TO THESE COMMENTS WERE SUBMITTED IN AMENDMENT DATED OCTOBER 2, 2001: FIRM'S RESPONSE ARE IN ITALICS FOLLOWING EACH DEFICIENCY

The following deficiencies pertain to the environmental assessment (EA) dated August 2000. Please provide a revised EA that incorporates the changes. The appendices need not be resubmitted if there are no changes in them.

1. With respect to Section IV.D. of the July 1998 guidance entitled Environmental Assessment of Human Drug and Biologics Applications, please revise the EA (specifically for the water solubility, ionization constant, partition coefficient, and vapor pressure) so that the environmental assessment includes a description of the test method. The reference to the drug master file is not sufficient. The test method description should be sufficient for a reviewer to determine the scientific merit of the methodology. For example, the methodology used to determine water solubility should be identified, along with the temperature and pH at which the solubility was determined. If actual studies were not done (e.g., vapor pressure), please provide the basis for the statements.

   In the amendment dated October 2, 2001, the firm provides a Table that shows the physicochemical characteristics of gatifloxacin (water solubility, ionization constant, partition coefficient, and vapor pressure), plus a summary of the analytical test method used for determining each characteristic. In an October 9, 2001 fax, the firm gives permission that this table can be released under FOI. ADEQUATE

2. The confidential appendices indicate that the acute toxicity results are on the active ingredient basis, however, it is not clear from the data provided in the summary table whether or not the acute toxicity studies are based on the active ingredient as opposed to the hydrate. Please clarify and update the appropriate sections in the EA to reflect this calculation.

   In the amendment dated October 2, 2001, the firm states that for the fish and daphnia studies, the data are expressed as anyhydrous

drug. For the microbial inhibition studies, the data are expressed as the concentration of gatifloxacin sesquihydrate. ADEQUATE

3. On page 3 of the EA, you make the following statement: "Portions of the environmental assessment, including the appendices, are considered confidential by Bristol-Meyers Squibb Company, and should not be released under the Freedom of Information (FOI) Act. A separate, nonconfidential report releaseable under FOI is also provided." However, it is not clear what part of the submitted EA are confidential and nonconfidential. Please clearly identify the parts of the EA you consider nonconfidential when submitting the revised EA.

In the October 2, 2001 amendment, the firm clarifies that the first 19 pages of the EA are non-confidential and the remainder of the EA (Volume 3, Page 20-301 are confidential. The confidential section are Appendix 1: Production Volumes and Expected Environmental Concentrations and Appendix 2: Referenced Proprietary Documents (i.e., the study reports). ADEQUATE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Melissa Maust
10/10/01 09:56:15 AM
ENV ASSESSMENT

This is the second review in response to amendment dated October 2, 20
01. A FONSI is recommended.

Nancy Sager
10/10/01 11:02:00 AM
ENV ASSESSMENT

Yuan-Yuan Chiu
10/10/01 02:40:58 PM
CHEMIST
concurred